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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/695,597 | 10/28/2003 | Frank Himmelsbach | 1/1410 | 5362 |

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| EXAMINER | |
|---|---|
| BERCH, MARK L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | |

DATE MAILED: 10/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/695,597 | HIMMELSBACH ET AL. | |
| | Examiner | Art Unit | |
| | Mark L. Berch | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-7* is/are allowed.

6)☒ Claim(s) *8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/17/2006 has been entered.

Applicant's request filed 08/17/2006, for suspension of action in this application under 37 CFR 1.103(c) is denied as being improper. MPEP 709 (I)(B)(1) says that the request filed with the filing of a an RCE is to use the check box provided on the transmittal form PTO/SB/29 or PTO/SB/30, or is to be submitted on a separate paper. Neither was done; the request was on the same sheet as the request for an RCE, and no PTO/SB/29 or PTO/SB/30 was used.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is no way of knowing what the scope of these two claims are. Claim 8 refers to any "disease or condition associated with an increased DPP-IV activity." There is no such list of diseases; decades of research is involved in generating such understanding. Note

that this claim covers any kind of association. It covers not only diseases caused by increased DPP-IV activity, but also diseases or condition which themselves cause increased DPP-IV activity, which are frequently unknown. It does not require that the disease actually be responsive to reducing DPP-IV activity.

Claim 9 basically covers any disease where reduction of DPP-IV activity works. It will be the subject of a large amount of research over a period of decades to determine which diseases will in fact respond and which will not; this constitutes undue experimentation, and hence the claims is indefinite as well.

Claims 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for diabetes, obesity, and osteoarthritis, does not reasonably provide enablement for arthritis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.
The analysis is as follows:

(1) (a) Breadth of claims. Owing to the huge scope of the 4 primary variables, the claims cover trillions of compounds.

(b) Scope of diseases. As is established in the above rejection, this is unknown. The specification mentions type I and type II diabetes mellitus, diabetic complications, metabolic acidosis or ketosis, insulin resistance, dyslipidaemias of various origins, atherosclerosis and related diseases (whatever that might be), obesity, allograft transplantation and calcitonin-induced osteoporosis. The specification mentions arthritis. The term "arthritis" is a general term denoting inflammation of the joints, and may or may not involve inflammation of other parts of the body such as the nails. It mostly commonly refers to any of osteoarthritis, gouty arthritis, or rheumatoid arthritis. These are three totally different and unrelated disorders, which all have "arthritis" in their name and involve inflammation of the joints. Rheumatoid arthritis is an inflammatory disorder causing destruction of articular cartilage. It is an autoimmune condition where the body's immune system attacks its joints. In gouty arthritis, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Osteoarthritis is a degenerative cartilage disorder; cartilage breakdown causes bones to rub against each other. Causes include injuries, diseases such as Paget's disease, and long term obesity, but often the cause is unknown. Complicating matters further is that fibromyalgia is sometimes also intended to be included in the loose term "arthritis". There is also Psoriatic Arthritis (including DIP, and spondylitis) which is believed to be autoimmune in origin but is a separate disorder from Rheumatoid arthritis. There is also an assortment of infectious arthritis, i.e. arthritis caused by bacteria, rickettsiae, mycoplasmas, viruses (or vaccinations given to prevent viral infections), fungi, or

parasites. Included in this category are various types of septic arthritis, mycotic arthritis, and viral arthritis, such as rubella arthritis, Lyme arthritis, Mumps arthritis, arboviral arthritis, syphilitic arthritis, parvovirus arthritis, tuberculous arthritis, Varicella arthritis, gonococcal arthritis, rubella arthritis, Reiter's syndrome (which includes a form of arthritis commonly arising from infection by Chlamydia trachomatis) etc. These assorted disorders can arise from quite varied sources. Moreover, in addition to the above, CPDD (sometimes called pseudoosteoarthritis, or pseudogout) arises from Calcium Pyrophosphate Deposition. Systemic onset juvenile idiopathic arthritis (SOJIA), unlike rheumatoid arthritis, appears dependent on IL-1 and dendritic cell malfunction. Menopausal arthritis is due to ovarian hormonal deficiency. Still's disease has a substantial numbers of syptoms associated with it, and is presently cosndiered idiopathic. Neuropathic arthritis (which comes in several forms, such as Charcot's disease) can arise from sources as diverse as Diabetes Mellitus, Steroid treatment, Leprosy, Chronic alcoholism, Heavy metal poisoning and Neoplastic peripheral neuropathy. There is also type II collagen-induced arthritis (CIA). The specification also mentions preventing B-cell degeneration such as e.g. apoptosis or necrosis of pancreatic B-cells, and mentions improving or restoring the function of pancreatic cells and also increasing the number and size of pancreatic B-cells. Included also are a sedative or anxiety-relieving effect, favorably affecting catabolic states after operations or hormonal stress responses, and reducing mortality or morbidity after myocardial infarct. In addition, the compounds are alleged to be useful as diuretics or antihypertensives and treating acute renal failure. They are also suitable treatment of chronic inflammatory intestinal diseases. This is a category that the examiner presumes would include the numerous forms of Chronic Gastritis, including

Chronic Atral Gastritis, Chronic Atrophic Gastritis, Multifocal Atrophic Gastritis (MAG), chemical gastritis, Autoimmune Gastritis, *Helicobacter* gastritis, Infectious granulomatous gastritis, Hypertrophic gastritis, Chronic noninfectious granulomatous gastritis, Lymphocytic gastritis, Eosinophilic gastritis, Radiation gastritis, and ischemic gastritis. It would also include various forms of IBD, including Ulcerative colitis, Crohn's disease, lymphocytic colitis, collagenous colitis, and Behçet's Syndrome. The specification also mentions the treatment of infertility and for treating deficiencies of growth hormone which are associated with reduced stature. It should be noted in this regard that both claim 8 and claim 9 would involve not only treating these disorder, but preventing them in the first place, e.g. preventing a person from getting e.g. type I diabetes mellitus, Rheumatoid arthritis and Crohn's disease. In addition, claim 8 also covers disorders which cause the above list in the first place, since these would be "associated" with the increased DPP-IV seen in the e.g. arthritis, type II diabetes or obesity. Thus, for example, there are assorted metabolic disorders which cause obesity, Paget's disease can cause osteoarthritis, smoking which can cause atherosclerosis, so the treatment of all of these would also be covered by claim 8.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information on page 40 is incomplete, in that it is given in the form of mg, not mg/kg. Moreover, this is generic, the same for the many disorders covered by the specification, which are quite extensive. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for atherosclerosis, rheumatoid arthritis, or any other specific disease.

(4) State of the Prior Art: These compounds are 7-substituted xanthines with a particular substitution pattern at the 1-, 3- and 8-positions. So far as the examiner is aware, no 7-substituted xanthines of any kind have been used for the treatment of type I diabetes , mellitus rheumatoid arthritis, etc.

(5) Working Examples: There are none to the treatment of any disorder.

(6) Skill of those in the art: The skill level in rheumatoid arthritis is relatively low. Very few agents have been successfully used to treat RA itself, and these have all operated by the mechanism of α-TNF inhibition. There has been some research on the use of DPP-IV inhibitors for RA, but even as of 2005, after the instant filing date, the situation is still unclear. Moreover, some early positive results have recently been reassessed. In Busso et al., American Journal of Pathology 166:433-442 (2005), it is stated: "Paradoxically, although DPPIV inhibition was beneficial in experimental models of RA and multiple sclerosis, genetic deficiency of CD26 leads to exacerbation of these diseases: AIA was more severe in CD26-deficient mice (this study); similarly, EAE was exacerbated in CD26-knockout mice. The reasons for such discrepancy may be related to the additional effects of the inhibitors, able to act even in DPPIV-deficient animals suggesting that, besides DPPIV inhibition, these inhibitors may have other functional targets." In other words, the

beneficial effects seen in earlier studies are likely not to have arisen from DPPIV inhibition, but from the fact that the particular drugs used had "other functional targets." In particular, the paper goes on to suggest that the other target may be DPP8/9, i.e. that the drugs were not particular selective for DPP-IV. Thus, it is clear that, even as of 2005, it has not been established that inhibition of DPP-IV is of value in treating RA, and indeed, such a conclusion is inconsistent with the fact that AIA was more severe in CD26-deficient mice. As for prevention, RA is known not to be preventable. Most other disorders fair no better. IBD arises from a ranges of causes, known and unknown. Ulcerative colitis, Behçet's Syndrome and Crohn's disease, for example are idiopathic.

(7) The quantity of experimentation needed: Owing especially to factors 1, 4, 5, and 6, the amount is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The obviousness-type double patenting over claims 5-6 of copending Application No. 10639036 has been overcome by the elimination of the phenanthridinyl choice.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE

**FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).**

**A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.**

**Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.**

**If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.**

**Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).**

**Mark L. Berch**
**Primary Examiner**
**Art Unit 1624**

**9/21/06**